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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/046,833 | 03/24/1998 | DAKAI LIU | ENZ-56(DIV4) | 2594 |

28171 7590 12/19/2007

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| EXAMINER | |
|---|---|
| GUZO, DAVID | |
| ART UNIT | PAPER NUMBER |
| 1636 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 12/19/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/046,833 | LIU ET AL. | |
| | Examiner | Art Unit | |
| | David Guzo | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *91-111* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *91-111* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## Detailed Action

### 35 USC 101 Rejections

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 91-111 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 91 appears to be a product claim (a packaging cell) but the claim recites process steps whereby the product appears to be modified. The claim does not appear to be a product by process claim and hence the claim appears to be a product claim **and** a process claim, which is non-statutory. Claims 92-111 are rejected based upon their dependence upon claim 91.

### 35 USC 102 Rejections

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 91-94, 97-98,109, 110 and 111 are rejected under 35 U.S.C. 102(b) as being anticipated by Strair et al.

Applicants claim a packaging cell line for propagating a viral vector independent of a helper virus, said viral vector comprising a nucleic acid component and at least two different non-nucleic components, wherein one of said non-nucleic acid components has a tropism for said cell line and the other non-nucleic acid component has a tropism for a target cell which is different from said cell line, said nucleic acid component and said non-nucleic acid components being capable of forming a specific complex or complexes, wherein said sequence or sequences for the viral vector nucleic acid component is stably integrated in the genome of said cell line, and said sequence or sequences for the non-nucleic acid components of said viral vector are introduced into said packaging cell line by transient expression, episomal expression or stably integrated expression.

The examiner is interpreting the language of Claim 91 as follows: Claim 91 appears to be a composition claim reading on a packaging cell line. The claim contains intended use language which usually does not carry patentable weight in a composition claim. The claim recites non-nucleic acid properties of the viral vector wherein the recited properties of the viral vector may or may not be imparted to the vector by the packaging cell. For example, the tropism of the viral vector may be imparted after the viral vector is made by the packaging cell, i.e. the viral vector envelope may be conjugated with a compound which determines its tropism. The claim recites a process step which appears to indicate that the packaging cell line is modified (at some point in

time) to include sequences which encode the non-nucleic acid components. It is unclear if the results of the process step are intended to be part of the packaging cell line because they are not recited as a product by process but instead as some optional further modification of the claimed cell line.

When the intended use language (i.e. for propagating a viral vector independent of a helper virus...) is removed and the language describing the non-nucleic acid properties of the viral vector is removed and the process steps reciting modifying the packaging cell at some point in time with regard to introducing sequences for the non-nucleic acid components of the viral vector are removed, the claim reads on **a packaging cell wherein the nucleic acid sequence component of the viral vector is stably integrated in the genome of said cell line**. The claims will be examined based upon this interpretation.

Applicants use the term "derived from" with regard to nucleic acid sequences. Since the metes and bounds of this terminology are not defined (i.e. applicants do not recite the methodologies by which a sequence is derived from another sequence), the examiner interprets this language to mean that a sequence is derived from another sequence if it contains at least one nucleotide in common with the sequence from which it was derived.

Strair et al. (Nucleic Acids Res., 1993, Vol. 21, No. 20, pp. 4836-4842, see whole article, particularly the Abstract, Figs. 1 and 4, pp. 4839-4840) recites a packaging cell line (H9/HIV-gpt or HeLa T4/HIV-LacZ) comprising a viral vector (HIV vector) wherein the nucleic acid component of the vector is stably integrated into the

genome of the cell line. The vector can be rescued by supplying the functions missing from the integrated HIV vectors and therefore the cells are packaging cells. The viral vector DNA comprises sequences "derived from" cDNA (i.e. LacZ or gpt gene sequence) wherein said sequences can be expressed in a target cell such as a T cell. Strair et al. therefore teaches the claimed invention.

Claims 91, 93-98 and 109-111 are rejected under 35 U.S.C. 102(e) as being anticipated by Flotte et al.

Applicants' invention is as described above. Additionally, applicants that the packaging cell is from a non-human animal or a murine species.

Flotte et al. (US 5,658,776, issued 8/19/1997, filed 6/7/1995, see whole document, particularly columns 9-13, Example 7 and Claims 1-15) teaches packaging cell lines (which can be human cells such as HeLa cells, A549 cells, etc. or can be from rodents (i.e. murine cells) comprising a AAV vector wherein the nucleic acid component of the vector is stably integrated into the genome of the cell line. The vector can be rescued by supplying the functions required for virion morphogenesis and replication and therefore the cells are packaging cells. The viral vector DNA comprises sequences "derived from" cDNA (i.e. neo gene sequence) wherein said sequences can be expressed in a target cell such as a human epithelial cell or other cells infected by AAV. Flotte et al. therefore teaches the claimed invention.

**35 USC 103(a) Rejections**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 99-102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Flotte et al. in view of Chatterjee et al.

Applicants claim the packaging cell line and viral vector as defined in the above 35 USC 102 rejections. Additionally, applicants recite that the viral vector encodes for an antisense RNA targeted against a mRNA coding for an undesirable protein in a target cell as well as a sequence coding for a protein of interest.

Flotte et al. is applied as above. Flotte et al. does not teach expression of antisense sequences by viral vectors but indicates that AAV vectors have been used to express antisense sequences in the prior art.

Chatterjee et al. (US 5,474,935, issued 12/12/1995, see whole document, particularly Claims 1-11, columns 8-12, etc.) teaches the use of AAV vectors to express antisense RNAs targeted against mRNAs coding for undesirable proteins (i.e. ICP4 of HSV, etc.) and wherein the vectors can also comprise a gene of interest (i.e. neo gene).

The ordinary skilled artisan, seeking to generate viral vector packaging cells capable of generating AAV vectors capable of expressing an antisense sequence directed against the mRNA from an undesirable gene in a target cell, would have been motivated to combine the teachings of Flotte et al. on the generation of recombinant AAV vector packaging cells with the teachings of Chatterjee et al. on the AAV vectors and packaging cells which generate AAV vectors capable of expressing antisense sequences targeted against mRNAs from undesirable genes (i.e. ICP4 form HSV) in target cells because the expression of antisense sequences targeted against undesirable genes in target cells has been a well known technique to inhibit the growth of undesirable target cells or inhibit virus replication, etc. It would have been obvious for the ordinary skilled artisan to do this because use of viral (AAV) vectors to deliver antisense sequences to target cells, in the context of treatment of diseases, was well known in the art (see Chatterjee et al.) and was a standard use of AAV vectors. Given the teachings of the cited prior art and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 103-104 and 106-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Flotte et al. in view of Chatterjee et al. and further in view of Dietz et al.

Applicants' invention is as described above. In addition, applicants claim a packaging cell line comprising a viral vector which encodes an antisense RNA targeted against a mRNA coding for an undesirable protein in a target cell and wherein the antisense RNA can be a part of a chimeric RNA molecule that comprises sequences from small nuclear RNAs (for example, U1 snRNA).

Flotte et al. and Chatterjee et al. are applied as above. Neither reference teaches a viral vector which encodes an antisense RNA that can be a part of a chimeric RNA molecule that comprises sequences from small nuclear RNAs (snRNAs).

The ordinary skilled artisan, seeking to develop packaging cell lines capable of generating viral (AAV) vectors capable of expressing an antisense sequence or a chimeric antisense RNA molecule, would have been motivated to combine the teachings of Flotte et al. and Chatterjee et al. on the generation of AAV packaging cell lines comprising stably integrated AAV vectors capable of expressing antisense sequences targeted against undesirable targets with the teachings of Dietz concerning the use of viral (retroviral) vectors to express chimeric antisense sequences targeted against undesirable genes in target cells because the expression of antisense sequences targeted against undesirable genes was a well known technique in molecule biology and use of viral vectors to deliver chimeric RNAs (comprising antisense and snRNA sequences) to target cells was likewise known and desirable because Dietz

teaches that said chimeric RNAs are more stable and more efficacious than non-chimeric RNAs. It would have been obvious for the ordinary skilled artisan to do this because delivery and expression of antisense sequences targeted against undesirable genes had been a well known technique in molecular biology (see Flotte et al. and Chatterjee et al.). It would further have been obvious for the ordinary skilled artisan to select chimeric RNAs encoding antisense sequences and snRNAs because Dietz teaches that said chimeric RNAs make superior delivery vehicles for delivering the antisense sequences to the target cells. Given the teachings of the cited prior art and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

**35 USC 112, 2nd Paragraph Rejections**

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims105 and 108 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 105 (and dependent claim 108) are unclear because there is no antecedent basis for the term "said antisense RNA" in claim 91. It is noted that claims 105 and 108 are not rejected under 35 USC 102 or 103(a) because the metes and bounds of the claims cannot be discerned.

The grounds of rejection applied in the previous Office Action are withdrawn.

Applicants' arguments pertaining to said rejections are therefore moot.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (571) 272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David Guzo
October 11, 2007

DAVID GUZO
PRIMARY EXAMINER